Developmental Cell
Previews

Dystroglycan and AMP Kinase: Polarity's Protectors when the Power Goes Out

Li Zhang,[1] Patricia Seo-Mayer,[1] and Michael J. Caplan[1,*]
[1]Department of Cellular and Molecular Physiology, Yale University School of Medicine, P.O. Box 208026, New Haven, CT 06525, USA
*Correspondence: michael.caplan@yale.edu
DOI 10.1016/j.devcel.2008.12.004

The AMP-stimulated protein kinase regulates epithelial polarity under conditions of energy depletion by phosphorylating the myosin regulatory light chain. In this issue of *Developmental Cell*, Mirouse et al. demonstrate that dystroglycan and perlecan, an extracellular matrix receptor and its ligand, help localize myosin regulatory light chain, making it available for phosphorylation by AMP kinase in response to energy stress.

The tasks of defining, maintaining and defending the composition of the body's inventory of internal compartments all fall to its contingent of polarized epithelial cells (Muth and Caplan, 2003). The cells' ability to become and stay polarized suggests that they detect physical cues from their environments and respond to these cues by creating the structural and functional asymmetries that characterize the polarized state. These cues derive primarily from contacts that each cell makes with its neighboring cells and with the extracellular matrix. The establishment of these contacts initiates a cascade of events involving activation of protein kinases and the assembly of protein complexes, which together ultimately lead to the demarcation and construction of the apical and basolateral domains of the plasma membrane.

Until recently, little was understood about the molecular components that integrate these cues and transduce their messages. The discovery that the activity of the LKB1 kinase is necessary and sufficient to induce polarization of both mammalian and *Drosophila* epithelial cells suggests that LKB1 plays a central role in these signaling processes (Baas et al., 2004). LKB1 is a master kinase that phosphorylates and modulates the activities of at least thirteen downstream effector kinases (Lizcano et al., 2004). The adenosine monophosphate stimulated protein kinase (AMPK) is one of these effectors, and data from several studies suggest that it is a key contributor to the polarizing influence of LKB1 (Lee et al., 2007; Mirouse et al., 2007; Zhang et al., 2006; Zheng and Cantley, 2007). As its name implies, AMPK is activated when cellular levels of AMP rise, which usually occurs under conditions of cellular energy depletion. How does a kinase that responds to cellular energy depletion fit into the scheme that controls epithelial polarization? The paper by Mirouse et al. (2009) in this issue of *Developmental Cell* reveals a new and interesting aspect of the solution to this question.

Mirouse et al. have previously shown that mutation of the gene encoding AMPK leads to loss of polarity in *Drosophila* epithelia subjected to energy stress (Mirouse et al., 2007). Lee et al. have found that myosin regulatory light chain (MRLC) is a key substrate for AMPK phosphorylation in the polarization of *Drosophila* epithelia (Lee et al., 2007). Expression of a mutagenized phosphomimetic form of MRLC can suppress the loss of epithelial polarity phenotypes associated with mutations in the genes encoding either LKB1 or AMPK. In the current paper, Mirouse et al. (2009) identify another participant in the AMPK pathway. In a series of clever and elegant *Drosophila* studies, they demonstrate that dystroglycan, a basolateral transmembrane protein, is a critical component of the pathway through which AMPK activity preserves polarity in the face of energy depletion. Dystroglycan is a receptor for the extracellular matrix component perlecan. Disruption of perlecan expression also results in a loss of epithelial polarity in energy depleted cells, strongly suggesting that dystroglycan and perlecan function together to transduce a spatial cue from the extracellular matrix to the epithelial polarization machinery. Through its cytoplasmic tail domain, dystroglycan interacts with the large and diverse Dystrophin-associated protein complex and the actin cytoskeleton. In dystroglycan null epithelial cells, MRLC is not appropriately localized and fails to become phosphorylated by AMPK in response to energy stress, consistent with the possibility that perlecan and dystroglycan exert their effects on epithelial polarity by ensuring that MRLC is localized in a manner that renders it susceptible to AMPK phosphorylation.

Alternatively, rather than simply being required for AMPK signaling, the appropriately localized dystroglycan-perlecan complex could also be a consequence of AMPK signaling, and its AMPK-dependent positioning may be a prerequisite for subsequent steps in the polarization cascade. According to this model, AMPK sends a message from inside the cell to the exterior through its influence on the localization of dystroglycan and, by extension, perlecan. This organizing influence on the extracellular matrix could then serve to send an organizing signal back to the cell interior that would help to coordinate subsequent steps in the polarization process (Figure 1). Precisely this sort of rather rococo paradigm has been shown to account for the effect of the small GTPase Rac1 on the polarization of renal epithelial cells grown in three-dimensional cultures (O'Brien et al., 2001). Rac1 is required for the appropriate organization of basolaterally secreted laminin in the extracellular matrix, which is in turn required to initiate the proper placement and assembly of the apical plasma membrane domain. This possibility is consistent with the previous observation that AMPK is indeed required for the restriction of dystroglycan to the basal surface of the basolateral plasma membrane under conditions of energy stress (Mirouse et al., 2007). As we learn more about AMPK signaling

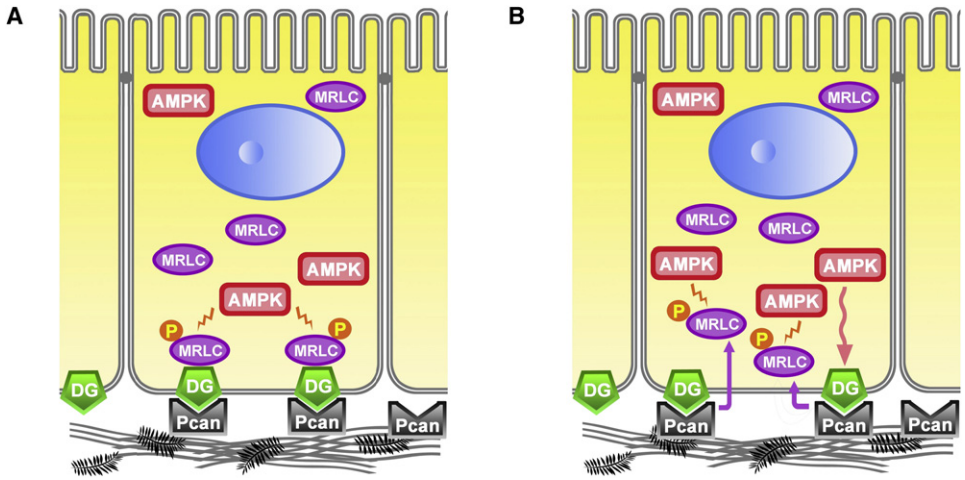

Figure 1. Where Do AMPK, DG, and MRLC Interact in the Polarization Pathway?
The scheme depicted in (A) corresponds to the model proposed in the accompanying paper by Mirouse et al. (2009). It posits that under conditions of energy depletion, DG helps to localize MRLC (myosin regulatory light chain) and thus makes it available for phosphorylation by AMPK. The alternative model shown in (B) suggests that AMPK acts to localize DG, which in turn organizes perlecan in the extracellular matrix, which then sends a polarizing message back into the cell interior that may facilitate MRLC phosphorylation by AMPK. This model is similar in many respects to the relationship that has been observed between Rac1 signaling, extracellular matrix components and epithelial polarity (O'Brien et al., 2001).

pathways in epithelial polarization, it will be interesting to see whether the function of dystroglycan is limited to localizing MLRC to make it available for AMPK phosphorylation or whether AMPK exploits dystroglycan and perlecan in an inside-outside-in signaling scheme that is analogous to the Rac1 and laminin relationship.

AMPK is thought to function as a cellular energy sensor that protects affected cells from damage due to energy deprivation by turning on processes involved in energy generation and turning off processes involving energy consumption (Hardie and Sakamoto, 2006). Since generating and maintaining epithelial polarity is clearly an energy-consuming undertaking, it is perhaps counterintuitive that AMPK responds to energy depletion by defending rather than dismantling the polarized state. This behavior suggests the interesting possibility that, in epithelial cells, AMPK responds to energy deprivation by initiating processes that are not limited to satisfying or reducing the energy needs of the epithelial cells themselves, but rather act in the interests of the organism as a whole. Polarized epithelial cells serve as intelligent boundaries that prevent the random diffusion-driven intermixing of an organism with its environment and that also mediate the selective import and export of biologically significant substances, often in opposition to steep concentration gradients (Muth and Caplan, 2003). Each of these responsibilities is critical to a metazoan organism's existence. The maintenance of epithelial polarization in the face of energy depletion thus represents a selfless act on the part of the epithelial cells, which respond to AMPK's awareness of their own energy deficits by marshaling their remaining resources to the performance of their most fundamental duty, the establishment and preservation of an organism's compositional integrity. The work of Mirouse et al. (2009) brings us a step closer to understanding how epithelial cells interpret the message sent by AMPK in this physiologically fascinating fashion.

REFERENCES

Baas, A.F., Kuipers, J., van der Wel, N.N., Batlle, E., Koerten, H.K., Peters, P.J., and Clevers, H.C. (2004). Cell *116*, 457–466.

Hardie, D.G., and Sakamoto, K. (2006). Physiology (Bethesda) *21*, 48–60.

Lee, J.H., Koh, H., Kim, M., Kim, Y., Lee, S.Y., Karess, R.E., Lee, S.H., Shong, M., Kim, J.M., Kim, J., and Chung, J. (2007). Nature *447*, 1017–1020.

Lizcano, J.M., Goransson, O., Toth, R., Deak, M., Morrice, N.A., Boudeau, J., Hawley, S.A., Udd, L., Makela, T.P., Hardie, D.G., and Alessi, D.R. (2004). EMBO J. *23*, 833–843.

Mirouse, V., Swick, L.L., Kazgan, N., St Johnston, D., and Brenman, J.E. (2007). J. Cell Biol. *177*, 387–392.

Mirouse, V., Christoforou, C.P., Fritsch, C., St Johnston, D., and Ray, R.P. (2009). Dev. Cell *16*, this issue, 83–92.

Muth, T.R., and Caplan, M.J. (2003). Annu. Rev. Cell Dev. Biol. *19*, 333–366.

O'Brien, L.E., Jou, T.S., Pollack, A.L., Zhang, Q., Hansen, S.H., Yurchenco, P., and Mostov, K.E. (2001). Nat. Cell Biol. *3*, 831–838.

Zhang, L., Li, J., Young, L.H., and Caplan, M.J. (2006). Proc. Natl. Acad. Sci. USA *103*, 17272–17277.

Zheng, B., and Cantley, L.C. (2007). Proc. Natl. Acad. Sci. USA *104*, 819–822.